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CARELLA, BYRNE, BAIN, GILFILLAN, CECCHI,
STEWART & OLSTEIN
6 BECKER FARM ROAD
ROSELAND, NJ 07068

EXAMINER

STRZELECKA, TERESA E

ART UNIT PAPER NUMBER

1637

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10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/920,571

Applicant(s)

LASKEN ET AL.

Examiner

Teresa E Strzelecka

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 October 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,5-9,11-15,20-25,27 and 29-61 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 5-9, 11-15, 20-25, 27, 29-61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- _____ If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Art Unit: 1637

DETAILED ACTION

1. This Office action is in response to an amendment filed on October 10, 2002.
2. Applicants cancelled claims 2-4, 10, 26, 28 and 62-64, and amended claims 1, 27, 29-31, 34, 35, 50, 56 and 59-61. Therefore claims 1, 5-9, 11-15, 20-25, 27, 29-61 are pending and will be examined.
3. This action is made non-final because of new grounds for rejection (35 USC 112, 2nd paragraph).

Response to Arguments

4. Applicant's arguments filed on October 3, 2002 have been fully considered but they are not persuasive. Applicants argue that the rejections under 35 USC 103(a) over two references by Lizardi have been overcome by amending claim 1 with the addition of limitations from claims 3 and 26. However, claim 26 was previously rejected over the Lizardi-1 reference, and claim 3 was rejected over the combination of Lizardi-1 and Lizardi-2 references, therefore these rejections were not overcome by Applicants amendment.

With respect to double-patenting, claims 3 and 26 of the U.S. Patent 6,323,009 are drawn to a method in which the primers are random and various dNTPs are used, therefore the double patenting rejection is maintained.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
6. Claims 1, 5-9, 11-15, 20-25, 27, 29-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Art Unit: 1637

A) Claim 1 is indefinite over the recitation of the limitations "... dTTP, dCTP, dATP, dGTP, dUTP, a naturally occurring dNTP different from the foregoing, an analog of a dNTP, and a dNTP having a universal base..." (emphasis added). It is not clear what is encompassed by the underlined terms. Applicants have not defined a "naturally occurring dNTP different from dTTP, dCTP, dATP, dGTP or dUTP", or dNTP analog, or a dNTP having a universal base.

B) Claim 39 recites the limitation "said target DNA" in line 2. There is insufficient antecedent basis for this limitation in the claim.

C) Claim 39 is indefinite over the recitation of the limitation "... said target DNA is selected from the group consisting of linear DNA, ...cDNA". If the term "target DNA" means amplification target circle, then this term is not further limiting claim 1, since linear DNA is not circular, and most cDNA molecules are not circular either.

D) Claim 50 recites the limitations "the 3'-terminal nucleotide" in line 1 and "the primer" in line 2. There is insufficient antecedent basis for these limitations in the claim.

E) Claim 54 recites the limitation "said target DNA" in line 3. There is insufficient antecedent basis for this limitation in the claim.

F) Claim 54 is indefinite over the recitation of the limitation "... said target DNA is selected from the group consisting of linear DNA, ...cDNA". If the term "target DNA" means amplification target circle, then this term is not further limiting claim 1, since linear DNA is not circular, and most cDNA molecules are not circular either.

G) Regarding claim 56 and 61 (dependent on claim 56), the phrase "such as" renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Art Unit: 1637

H) Claim 60 is indefinite over the recitation of the limitation "... a linear DNA target is used instead of ATC". Since the method of claim 1 is drawn to amplification of circular molecules, incorporation of this limitation would result in a different method being performed.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 1, 5-7, 11-14, 20-25, 27, 29, 31, 33, 35-40, 42, 44, 45, 48-54, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), referred to as Lizardi-1, and Lizardi-2 (U.S. Patent No. 6,124,120).

A) Lizardi-1 teaches amplification of circular DNA molecule by a rolling circle method .

The rolling circle amplification (RCA) involves hybridization of a primer to amplification target circle (ATC) followed by amplification using strand-displacing DNA polymerase (column 19, lines 20-31), resulting in a DNA molecule with multiple repeats of the ATC, usually referred to as tandem sequences DNA (TS-DNA).

In one embodiment of the amplification, strand displacement cascade amplification, (SDCA), secondary and tertiary primers are used, with sequences complementary to the ATC (col. 25, lines 36-49). The SDCA can be performed simultaneously with RCA, resulting in exponential amplification (col. 28, lines 8-18; col. 26, lines 61-66).

The primers are from 10 to 35 nucleotides long (col. 10, line 14).

Art Unit: 1637

The primers can contain a region at the 5'-end which is non-complementary to the ATC (col. 10, lines 16-22).

The ATC is a circular, single-stranded DNA molecule, of 40 to 1,000 nucleotides (col. 9, lines 25-29).

The ATC can be derived from a single-stranded bacteriophage (col. 35, lines 50-59).

Radioactive nucleotides can be used in the amplification (col. 21, lines 22-25).

Primers may include modified nucleotides to make them exonuclease-resistant. The phosphorothioate nucleotides can be positioned at the 5'-end of the primer (col. 10, lines 24-28; col. 13, lines 27-31).

Fluorescence-labeled nucleotides can be used (col. 11, lines 2-5).

The DNA polymerases to be used include: bacteriophage ϕ 29 DNA polymerase, phage M2 DNA polymerase, VENT DNA polymerase, Klenow fragment of DNA polymerase I, T5 DNA polymerase, PRD1 DNA polymerase, T4 DNA polymerase holoenzyme (col. 17, lines 66-67, col. 18, lines 1-11).

Lizardi-1 teaches oligonucleotides attached to solid support, including glass (col. 14, lines 34-43, 65-67; col. 15, lines 1-10).

B) Lizardi-1 does not teach random primers, linear DNA, duplex DNA with or without nicks, DNA larger than 10,000 nucleotides or DNA with unknown sequence.

C) Lizardi-2 teaches multiple strand displacement amplification (MSDA) method, in which multiple primers are used to amplify DNA strand of interest (col. 2, lines 25-53). The method can be used to amplify any target nucleic acid (col. 5, lines 21-25), including whole genomic DNA using random primers (col. 3, lines 6-10). The DNA molecules to be amplified can be very long, on the order of 50,000 nucleotides (col. 2, lines 64-67).

Art Unit: 1637

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have included random primers and DNA molecules of Lizardi-2 in the methods of Lizardi-1. The motivation to do so would have been that random primers allowed for amplification of unknown DNA sequences, and using double-stranded DNA targets broadened the range of amplifiable target DNAs.

9. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claim 1 above, and further in view of Sorge et al. (U.S. Patent No. 5,599,921).

A) Claim 8 is drawn to the multiple primers being hexamers, and claim 9 to multiple primers being octamers.

B) Lizardi-1 or Lizardi-2 do not teach hexamers or octamers as primers.

C) Sorge et al. teach families of oligonucleotides from 6 to 8 bp long for use as primers, with sequences substantially complementary to the target DNA (col. 4, lines 27-33; col. 12, lines 8-18).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used primers of Sorge et al. in the amplification method of Lizardi-1 and Lizardi-2. The motivation to do so would have been hexamers and octamers were used to construct of libraries of primers in large quantities for use in amplification reactions.

10. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claims 12 and 13 above.

A) Claim 15 is drawn to denaturing two strands of a duplex DNA circle in the amplification process.

B) Neither Lizardi-1 nor Lizardi-2 teach denaturation step of the duplex DNA circle.

It was well known and common knowledge in the art that amplification reaction involving primers and double-stranded DNA required separation of the two strands, usually achieved by denaturation. Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have added a denaturation step to the amplification reaction when amplifying double-stranded DNA.

11. Claims 32, 41, 46, 47 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claims 1, 38 and 44 above, and further in view of Skerra (Nucleic Acids Research, Vol. 20, pp. 3551-3554, 1992).

A) Claims 32 and 41 are drawn to a polymerase with 3' → 5' exonuclease activity, claim 46 to a modified nucleotide being a 3'-terminal nucleotide, claim 47 to the modified nucleotide being a phosphorothioate nucleotide and claim 59 to the use of a mixture of primers sensitive to and resistant to exonuclease activity.

B) Neither Lizardi-1 nor Lizardi-2 teach primers resistant to 3' → 5' exonuclease activity, the resistance being conferred by a phosphorothioate nucleotide at the 3'-end of the primer or the use of a mixture of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction.

C) Skerra teaches that incorporation of a phosphorothioate nucleotide at the 3'-end of the primer renders it inactive to the 3' → 5' exonuclease activity of DNA polymerases such as Vent and Pfu. The reference also teaches use of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction (page 3553, Fig. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used primers of Skerra with phosphorothioate nucleotides at the 3'-end in the amplification method of Lizardi-1 and Lizardi-2. The motivation to do so would have been that the

3'-end phosphorothioate nucleotide rendered the primers resistant to 3'→5' exonuclease activity the polymerase used in the reaction, resulting in an improved yield of the amplification product.

12. Claims 30, 34 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claims 1, 26 and 43 above, and further in view of Cummins et al. (Biochemistry, vol. 35, p. 8734-8741, 1996).

A) Claim 30 is drawn to the nuclease activity being due to endonuclease, claims 34 and 43 are drawn to the nuclease activity due to contaminating nuclease.

B) Neither Lizardi-1 nor Lizardi-2 teach nucleotides conferring resistance to endonuclease activity due to contaminating nucleases.

C) Cummins et al. teach oligonucleotides containing nucleotides with phosphorodithioate linkages which are resistant to nucleases in nuclear and cytoplasmic extracts (Abstract; Figure 1; page 8738, paragraphs 2-5; page 8739; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used phosphorodithioate-modified nucleotides of Cummins et al. in the method of Lizardi-1 and Lizardi-2. The motivation to do so, expressly provided by Cummins et al., would have been that these nucleotides conferred resistance to oligonucleotides present in nuclear and cytoplasmic extracts and in human serum.

13. Claims 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claim 1 above and further in view of Sorge et al. (U.S. Patent No. 5,556,722).

A) Claim 55 is drawn to DNA polymerase without the 3'→5' exonuclease activity, and claim 56 to specific DNA polymerases not exhibiting this activity (e.g. Taq, Tfl, etc.)

B) Neither Lizardi-1 nor Lizardi-2 teach DNA polymerases without the 3'->5' exonuclease activity (exo(-)).

C) Sorge et al. teaches Taq DNA polymerase which lacks 3'->5' exonuclease activity (col. 5, lines 30-67; col. 6, lines 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used exo(-) Taq DNA polymerase in the method of Lizardi-1. The motivation to do so, expressly provided by Sorge et al., would have been that Taq polymerase was highly processive.

14. Claims 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi-1 and Lizardi-2 as applied to claim 1 above.

A) Claim 57 is drawn to the DNA polymerase being a reverse transcriptase and claim 58 to the ATC being RNA and the DNA polymerase being a reverse transcriptase.

B) Neither Lizardi-1 nor Lizardi-2 teach RNA targets or reverse transcriptase.

C) Lizardi-2 teaches that a target DNA can be any nucleic acid (col. 5, lines 21-25) and amplification of cDNA obtained from mRNA (col. 21, lines 14-20).

D) It was well known and common knowledge in the art at the time of the invention that cDNA was obtained from mRNA using reverse transcriptase.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have included RNA targets of Lizardi-2 in the amplification method of Lizardi-1. The motivation to do so would have been that RNA amplification provided a measure of gene expression in cells.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claims. See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

16. Claims 1, 5-9, 11-15, 20-25, 27 and 29-61 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 5-9, 11-15, 20-28, 30-61 of U.S. Patent No. 6,323,009. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claim 26 of the '009 patent is different from claim 1 of the current application in that it fails to disclose that the primers are random. However, the portion of the '009 patent that supports primers teaches that the primers may be either specific or random, with the random primers being especially useful (col. 7, lines 4-6).

Therefore it would have been obvious to one of ordinary skill in the art to modify the method of claim 26 of the '009 patent to use random primers. The motivation to do so would have

Application/Control Number: 09/920,571

Art Unit: 1637

been that using random primers allowed amplification of target nucleic acids with unknown sequences.

Claims 5-9, 11-15, 20-25, 28 and 30-61 of the '009 patent are dependent claims corresponding to dependent claims 5-9, 11-15, 20-25, 27 and 29-61 of the current application.

Conclusion


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
December 18, 2002

TS


KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

12/19/02